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SUGGESTIVE EVIDENCE FOR A DA D_3-RECEPTOR MEDIATED INCREASE IN THE RELEASE OF OXYTOCIN IN THE MALE RAT. K. Uvnäs-Moberg,[1] P. Alster,[1] V. Hillegaart,[1] S. Ahlenius.[1,2] Department of Physiology & Pharmacology, Division of Pharmacology[1], Karolinska Institute, S-171 77 Stockholm, and Department of Biochemical & Behavioral Pharmacology[2], Astra Arcus AB, S-151 85 Södertälje, Sweden.

It has been shown that the dopamine (DA) receptor agonist apomorphine produces increased plasma levels of oxytocin in male rats (Melis et al., Neurosci Lett 98:351, 1989). Dopamine receptors are generally grouped into two major, G protein-coupled, receptor families: DA D_1 (D_{1A} and $D_{5/1B}$) and DA D_2 (D_{2S} D_{2L} D_3 and D_4). Apomorphine as a DA receptor agonist has little selectivity between and within these DA receptor families (see e.g. Gingrich and Caron, Ann Rev Neurosci 16:299, 1993). In the present study we have examined the possible role of DA D_2 and D_3 receptors in the mediation of oxytocin release by comparing the effects of two DA D_3 receptor preferring agonists, (±)7-hydroxy-2-(di-n-propylamino(tetralin (7-OH-DPAT) and quinpirole, with effects produced by the DA D_2 receptor preferring agonist bromocriptine. Since it has been shown that pituitary DA receptors regulating prolactin release are of the DA D_2 subtype exclusively (Sokoloff et al., Drug Res 42:224, 1992), the effects of these agents on plasma oxytocin were compared with effects on plasma prolactin levels. The results demonstrate that the DA D_3 receptor preferring agonists quinpirole (0.5-8.0 mg kg^{-1} sc) and 7-OH-DPAT (0.2-3.2 mg kg^{-1} sc), but not the preferential DA D_2 receptor agonist bromocriptine (2.0-32.0 mg kg^{-1} sc), produced increased plasma oxytocin levels in the rat. In keeping with their affinity for the DA D_2 receptor, all three compounds produced a marked suppression of plasma prolactin levels in their respective dose range. It is suggested that DA D_3 receptors are involved in mechanisms regulating oxytocin secretion in the rat. These receptors may be localized directly on the magnocellular neurons of the paraventricular nucleus of the hypothalamus since there is evidence that DA can directly activate such neurons (Mason, Brain Res 267:113, 1983).

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CLONING REVEALS THAT BOVINE NEUROPEPTIDE FF AND NEUROPEPTIDE AF ARE GENERATED FROM THE SAME PRECURSOR. F.S. Vilim, E. Ziff. HHMI and Dept. of Biochem. NYU Med. Center 550 First Ave NY, NY, 10016.

NPFF (8-mer) and NPAF (18-mer) are mammalian neuropeptides related to the invertebrate neuropeptide FMRFamide which may be involved in pain sensitivity, opiate tolerance and opiate addiction in mammals. The amino acid sequence of these neuropeptides was published in 1985, but the precursor for these has not been identified until now. We have used degenerate oligo based PCR to identify the exact sequence encoding the 18-mer peptide NPAF. An oligo generated to an internal coding sequence, along with an oligo to the flanking vector region, was used in PCR from a Bovine brainstem cDNA library. This yielded 350 base pairs of upstream sequence and contained the NPFF amino acid sequence in frame with the NPAF sequence. The in frame upstream amino acid sequence extended to a hydrophobic signal peptide sequence, but ended there without revealing the initiator methionine or the 5' untranslated region. An oligo was generated to the upstream sequence and used, along with another oligo to the flanking vector region, to identify the sequence downstream to the NPAF coding sequence. NPAF is flanked by a C terminal glycine, which serves as the amide donor, followed by two lysines and a stop codon. The 3' untranslated region is short (86 bp to the poly A tail) and contains a polyadenylation signal. NPFF is also flanked by a C terminal glycine, which serves as the amide donor and an Arg-Asn, which is a preferred site for enzymatic cleavage. The location of putative N terminal cleavage sites suggest that the initial forms of both peptides are somewhat longer (NPFF = 11mer, and NPAF = 22mer), or are subject to further enzymatic cleavage. We are currently using 5' RACE to identify the rest of the upstream sequence. We plan to clone rat, mouse and human NPFF precursors, study their regulation in rat, generate null mutants in mice, and investigate the role of these peptides in pain sensitivity, opiate tolerance, and opiate addiction.

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